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Evaluation of response to treatment in iron deficiency anemia after coronary artery bypasses graft surgery

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ABSTRACT

Introduction: Anemia is a decrease in hemoglobin and red blood cells that decreases oxygen-carrying capacity. There are different types of anemia, the most common of which is iron deficiency anemia. Anemia is common in patients undergoing surgery, especially cardiac surgery. Therefore, the goal of this research was to evaluation of the response to treatment in iron deficiency anemia after CABG surgery. *Materials and Methods:* This study was performed on patients with CABG surgery at the Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. The data collection tool was a questionnaire. For patients who were anemic (Hb<11gr/dl) at discharge from the ICU, standard oral treatment with ferrous sulfate was started three times daily. To evaluate the response to treatment, hematological tests were followed at discharge from the ICU, one week, three weeks and three months after treatment. Data analysis was carried-out by Chi-square, Mann-Whitney test, and ANOVA test. *Results:* 380 patients underwent on CABG surgery, of which 110 had iron deficiency anemia at discharge from ICU. Of these 110 patients, 32 could not be followed up due to the Covid 19 pandemic, Forty-eight patients responded to standard oral iron therapy, and 30 did not respond adequately to various causes. Hemoglobin, hematocrit, ferritin, Iron, transferin saturation (TS) and reticulocyte levels in patients who responded appropriately to treatment increased significantly during treatment. *Conclusion:* Although the standard treatment for iron deficiency anemia is oral iron, but there are several factors such as a pandemic, gastrointestinal complications, long duration of treatment, and cultural problems which make the effectiveness of oral treatment questionable, thus intravenous iron should be considered in certain conditions.

Keywords: Iron deficiency anemia, Treatment, CABG surgery.

1. INTRODUCTION

Anemia is described by the WHO as circulating hemoglobin (Hb) below 130 g/dl for men and 120 g/dl for women (Murphy, 2011). Anemia can affect up to

a quarter of the world's population and is more common in the elderly or in patients with a variety of diseases (Musallam et al., 2011). Anemia is present in one-third of all patients undergoing surgery (Paone, 2018), but is more common in cardiac surgery (Möhnle et al., 2011). The causes for this higher outbreak are not known in patients undergoing cardiac surgery and maybe related to comorbidities, medication, or cardiovascular disease (Paone, 2018). The most common anemia in the world is iron deficiency anemia and the superlative usual reason of the iron deficiency is blood loss. Iron deficiency is characterized by the presence of hypochromic, and microcytic red blood cells that reflect an absolute deficiency of iron due to depletion of the body's iron stores (Aung et al., 2013).

Postoperative anemia is a popular complication in major surgeries, especially open heart surgeries (Goddard et al., 2011) which can be caused by excessive intraoperative hemorrhage, hemodilution, intraoperative inflammatory responses, blood transfusion (Exacerbating inflammatory responses and pump effects on coagulation factors and platelets), and the initiation of postoperative anticoagulants (Sanders et al., 2011). Since blood transfusion is recommended only in patients with severe anemia or in patients with hemodynamic instability, the prevalence of this complication have increased (Ferraris et al., 2012). Postoperative anemia is generally an acute condition that may improve on its own. However, a number of studies have reported that nearly 30% of patients suffered from anemia for up to a month after surgery. The prevalence of this complication in the first days after surgery has been reported up to about 99% (Karkouti et al., 2012). On the other hand, anemia is the main hazard factor in increasing mortality (between 1.4 and 3.4 times); its treatment is important in preventing postoperative mortality and reducing other debilitating complications (Elmistekawy et al., 2013). In addition to increased mortality, research has shown a direct link between anemia and an increased risk of heart failure. These side effects are especially seen in patients with a HB level of less than 11 g/dL (Williams et al., 2013). Therefore, it is reasonable to use methods such as injecting recombinant erythropoietin and administering oral and intravenous iron to prevent the complications of iron deficiency anemia and reduce mortality in patients who have undergone open heart surgery (Cladellas et al., 2012). In this study, we first assessed our patients' response to standard oral iron therapy to replace intravenous iron therapy if there was no adequate response.

2. MATERIALS AND METHODS

This study was performed on adult patients who underwent coronary artery bypass graft surgery at Rajaie Cardiovascular Medical and Research Center, Tehran, Iran from May to November 2020. The data collection tool was a questionnaire that was completed using interviews, observations and checklists. Patients who met the inclusion and exclusion criteria were included in the study.

Inclusion criteria include: hemoglobin less than 11 mg/dl at the time of discharge from the ICU and iron-deficiency anemia based on hematologic tests, having informed consent.

Exclusion criteria include: history of kidney disorders, autoimmune diseases, chronic infections, and patients with gastrointestinal diseases that impair iron absorption, history of bariatric surgery, bleeding disorders, thalassemia, various hemoglobinopathies, and malignancies. Also, patients with special diets, including vegetarianism, were excluded from the study.

Procedure

A total of 380 patients were operated, 110 of them had iron deficiency anemia when discharged from the ICU and included in the study. Then patient demographic information and surgical details (number of grafts, clamp time, pump time, transfusion during and after surgery) and hematological parameters (Hb, Hct, Retic count, Serum Iron, Ferritin, TIBC, TS, MCV, MCH and MCHC) was completed at regular intervals during ICU discharge, as well as one week, three weeks, and three months after treatment. For these patients, standard oral treatment with 60 mg ferrous sulfate tablets was started 3 times a day. To evaluate the response to treatment, hematological tests including Hb, Hct, Retic count, Serum Iron, Ferritin, TIBC, TS, MCV, MCH and MCHC were performed during ICU discharge, one week, three weeks, and three months after treatment. Follow-up of the post-discharge process was through follow-up visits to the heart clinic and telephone calls. An instruction was given to the patient or to the patient's informant, containing complete explanations of the iron tablets use. In this sheet, the number of days and the number of daily use of the pill were specified and the sheet was completed by the patient or his/her companion with each use of the drug.

Data analysis

For continuous data, SW test was used and KS was also applied for checking non-normally distributed data. If the data are normally distributed, the standard deviation and mean were used to describe the data, while, the mean and the inter-quarter distance were used as descriptive indicators, if the data are no normally distributed. Unpaired t-test was used to compare groups with normal distribution and Mann-Whitney test was used in groups with non-normally distributed data. Relative frequency and

relative frequency percentage were used to describe qualitative traits. Chi Square test was used to compare frequencies. The repeated measures ANOVA were also used to evaluate quantitative longitudinal data.

Ethical considerations

A written letter of introduction was received from the university officials. A written letter of introduction was received from the officials of the selected research centers. The aim of the research was explained to all research units and written consent was obtained from them. Information of all patients was kept confidential by the project manager. In all stages of the research, the Declarations of Helsinki and Ethics Research Committees of the University of Medical Sciences were taken into account. The project was carried out after approval by the Research Council of the Medical School and receiving the code of ethics (IR.IUMS.FMD.REC.1399078).

3. RESULTS

A total of 110 patients with iron deficiency anemia were included in the study, of which 32 patients are not able to follow up because of Coronavirus Disease (COVID-19) pandemic. Of the remaining 78 patients, 48 responded to treatment. There were also 30 cases of non-response to treatment, due to various reasons such as refusing medication, digestive problems, and not having a culture of taking iron pills for a full three months. Table 1 showed the results of non-parametric Friedman test for repetitive measurements that the difference in the mean hemoglobin, hematocrit, reticulocyte, iron, TIBC, transferrin saturation (TS), MCV and MCHC at the measured times was significant at 95% confidence level ($P < 0.05$), while ferritin and MCH were not found to be significant at 95% level ($P > 0.05$).

Table 1 Comparison of hematological variables at set intervals

Variable	Number	Median	IQR	P-value
(g/dl) (Hb)				
Discharge from ICU	78	9.0	0.5	< 0.001
One week after treatment	78	9.6	0.6	
Three weeks after treatment	78	10.2	0.6	
Three months after treatment	78	11.7	2.2	
(Hct) (%)				
Discharge from ICU	78	28.9	1.1	< 0.001
One week after treatment	78	29.15	2.0	
Three weeks after treatment	78	31.9	3.0	
Three months after treatment	78	34.9	5.1	
(Retic count) (%)				P-value
Discharge from ICU	78	1.3	0.4	<0.001
One week after treatment	78	1.4	0.4	
Three weeks after treatment	78	1.5	0.4	
Three months after treatment	78	1.6	0.3	
(Fe)				P-value
Discharge from ICU	78	59.0	19.0	< 0.001
One week after treatment	78	64.0	16.0	
Three weeks after treatment	78	71.0	18.0	
Three months after treatment	78	80.0	30.0	
(Ferritin)				P-value
Discharge from ICU	78	170	85	0.168
One week after treatment	78	168	70	
Three weeks after treatment	78	153	58	
Three months after treatment	78	162	75	

(Ts) (%)				P-value
Discharge from ICU	78	16.6	30.6	<0.001
One week after treatment	78	18.0	3.2	
Three weeks after treatment	78	20.4	4.6	
Three months after treatment	78	24.0	11.3	
(FL) (MCV)				P-value
Discharge from ICU	78	83	8.3	0.038
One week after treatment	78	80.9	5.0	
Three weeks after treatment	78	80	3.0	
Three months after treatment	78	81	3.0	
(pg) (MCH)				P-value
Discharge from ICU	78	27.2	1.8	0.306
One week after treatment	78	27.9	2.8	
Three weeks after treatment	78	28	2.7	
Three months after treatment	78	28	2.1	
(g/dl) (MCHC)				P-value
Discharge from ICU	78	32.2	2.1	0.032
One week after treatment	78	32.3	2.0	
Three weeks after treatment	78	33	1.2	
Three months after treatment	78	33	1.3	
(TIBC)				P-value
Discharge from ICU	78	350	58	<0.001
One week after treatment	78	330	86	
Three weeks after treatment	78	340	51	
Three months after treatment	78	390	30	

The Dunn test was used for multiple comparisons, the results of which are shown in Table 2. The mean of hemoglobin, hematocrit, reticulocyte, iron, transferrin, TIBC and MCV at the time of discharge from the ICU were statistically significant when compared with the mentioned variables one week, three weeks and three months after treatment. Thus, the mean of these variables at the time of discharge from the ICU was significantly higher. Mean hemoglobin, hematocrit, reticulocyte, iron, transferrin and MCHC showed a statistically significant difference one week after treatment compared to the mean of these variables at three weeks and three months after treatment.

The mean of hemoglobin, HCT, reticulocyte, iron and transferrin showed a statistically significant difference three weeks after treatment compared to the mean of these variables in three months after treatment. The mean MCV one week after treatment was statistically significantly different from the mean MCV at three months after treatment. The mean MCHC at ICU discharged was statistically significantly different from the mean erythrocyte hemoglobin concentration three weeks and three months after treatment.

Table 2 Post Hoc comparison results based on Dunn test

Hb		P-value
ICU Discharge of	One week after treatment	.0000
	Three weeks after treatment	.0000
	Three months after treatment	.0110
One week after treatment	Three weeks after treatment	.0000
	Three months after treatment	.0280
Three weeks after treatment	Three months after treatment	.0640
Hct		P-value
	One week after treatment	.0010

ICU Discharge of	Three weeks after treatment	.0000
	Three months after treatment	.0000
One week after treatment	Three weeks after treatment	.0000
	Three months after treatment	.0000
Three weeks after treatment	Three months after treatment	.0000
Retic count		P-value
ICU Discharge of	One week after treatment	.0020
	Three weeks after treatment	.0000
	Three months after treatment	.0000
One week after treatment	Three weeks after treatment	.0010
	Three months after treatment	.0000
Three weeks after treatment	Three months after treatment	.0000
Fe		P-value
ICU Discharge of	One week after treatment	.0000
	Three weeks after treatment	.0000
	Three months after treatment	.0000
One week after treatment	Three weeks after treatment	.0000
	Three months after treatment	.0000
Three weeks after treatment	Three months after treatment	.0000
Total iron connection capacity		P-value
ICU Discharge of	One week after treatment	0.01
	Three weeks after treatment	0.002
	Three months after treatment	0.004
One week after treatment	Three weeks after treatment	0.189
	Three months after treatment	0.254
Three months after treatment	Three months after treatment	0.609
Percentage of transferrin saturation		P-value
ICU Discharge of	One week after treatment	.0000
	Three weeks after treatment	.0000
	Three months after treatment	.0000
One week after treatment	Three weeks after treatment	.0000
	Three months after treatment	.0000
Three months after treatment	Three months after treatment	.0000
Medium volume of red blood cells		P-value
ICU Discharge of	One week after treatment	.0000
	Three weeks after treatment	.0080
	Three months after treatment	.0120
One week after treatment	Three weeks after treatment	.0840
	Three months after treatment	.0270
Three weeks after treatment	Three months after treatment	.7620
Mean red blood cell hemoglobin concentration		P-value
ICU Discharge of	One week after treatment	.1000
	Three weeks after treatment	.0000
	Three months after treatment	.0040
One week after treatment	Three weeks after treatment	.0060
	Three months after treatment	.0360
Three weeks after treatment	Three months after treatment	0.551

The results of Mann-Whitney test (Table 3 & figure 1) showed that the mean hemoglobin, mean erythrocyte volume, iron, HCT and mean HB in the respondents were statistically significant one week after treatment compared to those who did not respond (P <0.05) and is more common in subjects who responded to treatment.

Table 3 Comparison of the studied variables in the patients who responded to treatment and those who did not respond to treatment within a week of treatment

Variable	Response to therapy		P-value
	Yes	No	
Mean red blood cell hemoglobin concentration one week after treatment	32.85± 2.0	32.20± 1.9	.071 *0
Average hemoglobin in the blood one week after treatment	28.00± 2.3	27.00 ±1.9	.010 *0
Average red blood cell volume one week after treatment	81.00±6.3	78.00±6.5	.008*0
Percentage of Ts in one week after treatment	18.45±6.3	17.90±1.9	.352 *0
Total iron binding capacity one week after treatment	359.50 ±77.0	324.00± 88.0	.087 *0
Ferritin one week after treatment	169.00 ± 71.8	149.00±64.0	.545 *0
Iron one week after treatment	67.00±19.0	56.00 ±17.0	.005 *0
Reticulocytes one week after treatment	1.40 ± .5	1.50± .4	.136 *0
Hematocrit one week after treatment	29.90±2.3	28.90± 2.9	.005 *0
Hemoglobin one week after treatment	9.70± .5	9.10± 0.9	<00.1*

*Mann Whitney Test

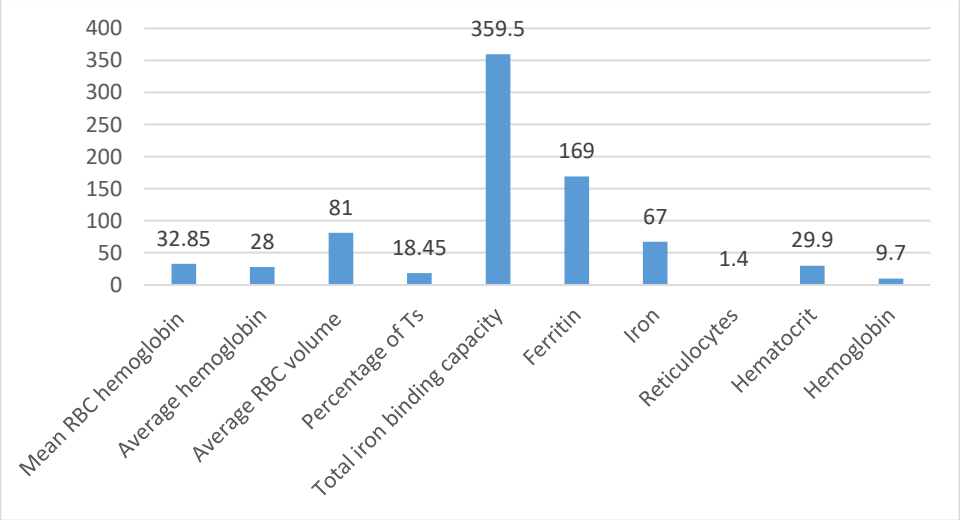

Figure 1 Comparison of the studied variables in the patients who responded to treatment

The results of Mann-Whitney and independent t-test showed that three weeks after treatment the mean hemoglobin concentration of red blood cells, mean erythrocyte volume, mean saturation of transferrin, iron, HCT and mean HB were significantly different in those who responded to treatment as compared to those who did not respond to treatment (P <0.05, Table 4), where these variables were greater in patients who responded to treatment.

Table 4 Comparison of studied variables in two groups of patients who responded to treatment and those who did not respond in three weeks after treatment

Variable	Response to therapy		P-value
	Yes	No	
Mean erythrocyte hemoglobin concentration three weeks after treatment	33.00±1.4	32.75± 1.1	.027 *0
Average hemoglobin in the blood three weeks after treatment	27.85± 2.6	28.00 ±2.9	.911 *0
Mean red blood cell volume three weeks after treatment	81.00 ±3.25	79.95±4.0	.004 *0
Percentage of transferrin saturation in three weeks after treatment	21.75± 6.1	19.40 ±2.1	<.001 *
Total iron binding capacity three weeks after treatment	339.82±28.29	323.11±41.3	.066**0
Ferritin three weeks after treatment	154.50 ±52.0	142.00 ±57.0	0.360 *
Iron three weeks after treatment	75.50 ±20.0	61.00 ± 11.0	<.001 *
Reticulocytes three weeks after treatment	1.55± .4	1.50 ± .4	.221 *0
Hematocrit three weeks after treatment	32.49±2.27	30.15±2.03	<.001**
Hemoglobin three weeks after treatment	10.30± .7	9.85±1.1	<.001 *

**Independent Samples T-test *Mann Whitney Test

According to the Mann-Whitney test, the mean erythrocyte volume, transferrin saturation percentage, total binding capacity of iron, iron, reticulocytes, HCT and HB were statistically significant in those who responded to treatment three months after treatment, as compared to those who did not respond to treatment (P <0.05, Table 5), where these values are higher in patients who responded to treatment.

Table 5 Comparison of the studied variables in the two groups of patients who responded to treatment and those who did not respond to treatment in three months after treatment

Variable	Response to therapy		P-value
	Yes	No	
Mean erythrocyte hemoglobin concentration three months after treatment	33.00 ±2.0	32.90± 1.1	0.118
Mean hemoglobin in the blood three months after treatment	28.00± 2.2	28.90± 2.1	0.772
Mean blood red blood cell volume three months after treatment	81.90± 3.00	79.00±3.5	<.001
Percentage of Ts in three months after treatment	28.00±10.2	18.00 ±1.8	<.001
Total iron binding capacity three months after treatment	322.00±36.0	348.21±39.0	<.001
Ferritin three months after treatment	162.00±55.0	130.00 ±68.0	.195 0
Iron three months after treatment	94.00 ±25.0	65.00 ±8.0	<.001
Reticulocytes three months after treatment	1.70± .3	1.50 ± .8	.002 0
Hematocrit three months after treatment	35.00±3.50	30.00±4.1	<.001
Hemoglobin three months after treatment	11.90±1.1	9.80±.6	<.001

Mann Whitney Test

4. DISCUSSION

Anemia reduces hemoglobin and oxygen carrying capacity. The amount and volume of red blood cells decrease in this disease. There are different types of anemia, the most common of which is iron deficiency anemia. Anemia is popular in patients undergoing surgery, especially cardiac surgery. Anemia has postoperative complications that endanger the patient's life if not compensated (Stone et al., 2012). Therefore, the goal of this research was to evaluation of the response to standard treatment in iron deficiency anemia after CABG. The findings of this research have shown that the hemoglobin, hematocrit, serum iron, ferritin and RBC indexes of those who responded to treatment were statistically significantly different from those who did not respond to treatment, where they were rather in patients who have responded to therapy.

Various studies have been conducted in this regard. Beck-da-Silva et al., (2013) examined the effect of oral, intravenous iron loading in patients with heart failure and anemia, where they reported effectiveness of iron in both forms in reducing anemia. In the research by, Litton et al., (2013) examined the evidence for the use of intravenous iron injections to reduce transfusion rates, risk of infection, and HB levels. This study examined all the clinical evidence from studies performed in a wide range of conditions that showed the effectiveness of intravenous iron loading in reducing transfusion rates and increasing HB in patients. The effect of this drug was especially on HB level in patients who received iron injection with Erythropoiesis-stimulating agents and also in patients with lower initial serum ferritin levels (Litton et al., 2013). Another study by Okonko et al., (2008) found that intravenous iron loading increased practice valence and marks in patients with chronic heart failure and that the benefits were greater in anemic patients.

In a study conducted by Hulin et al., (2005) intravenous iron loading (5 mg/kg injection of Venofer) significantly improved anemia in pediatric heart surgery patients on day 5 following surgery, which was in line with our study. A study by Carlos Del Campo et al., (2019) assessed the need for oral iron therapy in 37 patients who underwent CABG surgery. On average, all patients received 2 bags of blood during the operation. Hematological tests were checked again 10 days after the operation. On the day of discharge, the patients were randomly divided into two groups. Group I received ferrous gluconate 3 times/day, for six weeks and the second group was the control group. After reviewing the results showed that there are no statistically significant differences between the two groups, thus oral iron therapy was not capable of modifying the hematologic picture (Del Campo et al., 1982).

Karkouti et al., (2006) investigated the effect of intravenous iron therapy lonely or in syntax with recombinant erythropoietin (600 U x kg (-1) on POD 1 and 3) on reducing postoperative anemia after cardiac or orthopedic surgery or heart surgery. HB levels were monitored for up to one week after surgery. The results showed that intravenous iron alone or in combination with EPO did not have much effect on early recovery from postoperative anemia up to one week after surgery. Another study by Madi-Jebara et al., (2004) showed that postoperative iv iron III-hydroxide sucrose complex (IHSC) alone or in combination with a low dose of recombinant r-HuEPO (300 U/kg) was not capable of correcting anemia after cardiac surgery using cardiopulmonary bypass in patients with postpump hemoglobin range of 7 and 10 g/dL.

Based on the statistical analysis performed in this study, the response to treatment with oral iron loading was observed, but what led us to use of intravenous iron loading was the percentage of response to treatment (about 61.5) As a matter of fact, 48 out of 78 anemic patients responded to treatment (non-respondent: 40%).

5. CONCLUSION

Although the standard treatment for iron deficiency anemia is oral iron, but there are several factors such as a pandemic, gastrointestinal complications, long duration of treatment, and cultural problems which make the effectiveness of oral treatment questionable, thus intravenous iron should be considered in certain conditions.

Authors'contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Ethical approval

IR.IUMS.FMD.REC.1399078.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Data and materials availability

All data associated with this study are present in the paper.

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